

REMARKS

Claims 1-3, 5-7, 11, 14-19, 21 and 22 were examined in the Office Action dated May 14, 2003 and were rejected under 35 U.S.C. §103(a) as unpatentable over EP 517,565 to Callegaro et al. (“Callegaro”) in view of Partidos et al., *Immunology* (1996) 89:483-487 (“Partidos”) and Koichiro, JPO 015163161, abstract (“Koichiro”). The Office asserts that Harlow and Lane, *Antibodies: A Laboratory Manual* (“Harlow”) teaches that “antigen can be absorbed on the surface for continuous presentation to the immune system.” Office Action, page 5. Applicants note that Harlow is not cited against the claims but is being used to evidence the state of the art. Callegaro is said to teach that hyaluronic acid is a widely used polymeric carrier for the steady release of pharmacologically active molecules into the body and that Partidos teaches LTK63 as an effective mucosal adjuvant. Office Action, page 5.

However, applicants continue to assert for reasons of record that the present claims are not obvious over the cited art. In particular, as previously explained, the fact that the primary reference, Callegaro, pertains to the delivery of therapeutic proteins as opposed to vaccine antigens is not inconsequential. The mechanisms of action of the two are completely different. Vaccine antigens are delivered in order to produce an immune response. Therapeutic proteins are not. Thus, one of skill in the art would not be motivated to combine the teachings of Callegaro with Partidos and Koichiro.

In order to highlight the differences between the present invention and the cited combination, applicants are providing the Declaration of Derek O’Hagan, Ph.D. (“the Declaration”), addressing the cited combination. Dr. O’Hagan has over 20 years of experience in particulate vaccine delivery systems, such as those claimed in the present application. As explained in paragraph 5 of the Declaration, Callegaro’s therapeutic proteins are provided in order to treat a disease or disorder and are not administered in order elicit an immune response. In fact, such a response is **highly undesirable** and considered unsafe in the therapeutic context. As Dr. O’Hagan explains, immunogenicity is one of the criteria the FDA examines in order to determine whether a drug is safe prior to approval. Thus, Dr. O’Hagan concludes: “I would not be led to use hyaluronic acid

microspheres for delivery of an antigen upon a reading of Callegaro. Rather, I would be led to believe that hyaluronic acid microspheres would be ineffective for eliciting an immune response and would therefore be ineffective in a vaccine context.” Moreover, in paragraph 6 of the Declaration, Dr. O’Hagan concludes that based on the fact that Callegaro relates to delivery of therapeutics, he would not be motivated to combine the use of LTK63 with Callegaro’s hyaluronic acid microspheres to arrive at a system that provides enhanced immunogenicity to an antigen delivered as claimed.

With respect to Koichiro, Dr. O’Hagan explains that this reference does not administer an additional adjuvant with the antigen and the hyaluronic acid. In fact, Dr. O’Hagan has found that a system using hyaluronic microspheres alone with an influenza antigen, without coadministered adjuvant, is ineffective at producing an immune response. See, paragraph 7 of the Declaration. As explained in the Declaration, the combination of an influenza antigen with a hyaluronic microsphere and a coadministered adjuvant produced an exceptionally potent immune response, while use of antigen with the hyaluronic microsphere alone did not elicit a significant immune response. Dr. O’Hagan concludes at paragraph 8 of the Declaration:

[I]t is my opinion that a skilled scientist working in the field of antigen delivery would not have considered delivering vaccine antigens from using hyaluronic acid microspheres as claimed from a reading of the combination of Callegaro, Partidos and Koichiro, and certainly would not have expected to see such increased antibody titers using the system as claimed.

Based on the foregoing, applicants submit that the cited combination fails to render the present claims obvious and withdrawal of this basis for rejection is respectfully requested.

CONCLUSION

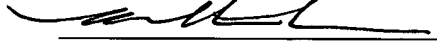
Applicants respectfully submit that the claims are novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

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Respectfully submitted,

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